#18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re-application of
Schwartz et al.

Group art Unit : 1625
Examiner :Seaman, D.M.M.

Serial N° : 09/622,199
Filed : May 31, 2001

For : Non-imidazole alkylamines as histamine H_3-receptor ligands and their therapeutic applications

DECLARATION UNDER RULE 132

Hon. Commissioner of Patents and Trademarks
WASHINGTON D.C. 20231

Sir :

I, Jean-Charles SCHWARTZ, residing at 9, villa Seurat, 75014 Paris, FRANCE ;

Declare and say :

I am citizen of France.

I am Professor and Chairman at Université René Descartes in Paris, member of the Institut Universitaire de France, member of the European Academy (Academia Europea), member of the French Academy of Sciences and author of over 700 publications in international journals.

I am an inventor of the above identified patent application. I am aware that the claims of the present patent application have been rejected for alleged lack of enablement.

This patent application claims a method of treatment using certain alkylamine compounds acting as ligands of the histamine H_3-receptors for treating various diseases.

The pharmacological studies reported in the patent application (page 150-153 of the PCT as published) clearly establish the interaction of compounds according to the invention with the H_3 receptor *in vitro* in rat and guinea pig. The effects of antagonists and agonists *in vivo* were estimated following the variation of the telemethylhistamine level induced.

I. Potential therapeutic applications of H_3 histamine receptor ligands

The role of the H_3 receptors as a presynaptic receptor regulating in an inhibitory fashion the release of histamine, various other monoamines and neuropeptides such as the tachykinins and CGRP[1] in brain as well as in peripheral tissues was discovered in my laboratory in 1983 [2].

---

[1] reviewed in Schwartz et al., Physiol Rev 1991, 71, 1; Hill et al. Pharmacol Rev. 1997, 49, 253 ; Schlicker et al Fundam. Clin. Pharmacol. 1994, 8, 128

[2] Arrang et al., Nature 1983, 302, 832

All known H_3-receptor agonists, including compounds of the present invention, inhibit the release of proinflammatory tachykinins and calcitonin-gene-related peptide (CGRP) from sensory C-fibres in a large variety of tissues, indirectly depress mast cell activity, and display "peripheral" anti-nociceptive activity[3].[4] From these actions at the level of airways derive potential applications in **asthma** and related inflammatory disorders.

In animal models of **migraine** consisting of electrical stimulation of the trigeminal nerve or capsaicin administration, plasma protein extravasation within the meninges is reduced by H_3-receptor agonist administration to the same extent as with administration of sumatriptan, a 5-HT_1-receptor agonist of established antimigraine activity. Initial experiments have already been performed on migraine patients using a low s.c. dose of histamine to activate H_3-receptors.

The anti-inflammatory activity of H_3-receptor agonists has been demonstrated in a large variety of tissues associated with antinociceptive effects and on some tests mostly connected to sensory C-fibres showing a gastric mucosal protective effect[5]. This constitutes a promising pattern for a novel class of **anti-inflammatory agents**.

These effects, taken together with the observed significant decrease of gastric acid secretion, may also be a new approach for the therapy of **gastric oesophageal reflux disease**. The potent anti-inflammatory activity of H_3-receptor agonists is shown in the capsaicin-induced model in tissues such as the gastrointestinal tract, the eyes, the airways or the bladder[3] [4]. In the latter organ, the effects indicate that the drugs will be useful to treat **cystitis** and **urinary incontinence**.

---

[3] Rouleau A. et al. J Pharmacol Exp Ther 1997; 281, 1085
[4] Rouleau A. et al. J Pharmacol Exp Ther 2000; 295, 219
[5] Bertaccini G. et al. Dig Dis Sci 1995, 40, 2052

For brain-penetrating H_3-receptor agonists, "**sedative**" properties in humans can be predicted from their inhibitory actions on monoaminergic (including histaminergic) neuron activity as well as behavioural changes in cats and rats [6 7 8].

Due to their influence on cardiac H_3-receptors and on noradrenaline release, agonists may offer a novel approach to **myocardial ischemia**

The most sustained behavioural effects of H_3-receptor antagonists, apparently occurring through the enhancement of endogenous histamine release, i.e. arousal, improved learning ability in aged rodents and improvement in attentional tasks all indicate a potential utility in the treatment of **mental disorders** such as the treatment of **Alzheimer's disease** symptomatology [6 7 8].

This conviction is reinforced by a least two sets of observations: tuberomammillary neurons seem relatively spared in Alzheimer's patients and tacrine is more active at inhibiting histamine than acetylcholine degradation in mouse brain *in vivo*.

The potential therapeutic use of H_3-receptor antagonists in status of **obesity** is indicated by the appetite suppressing effects of these agents in rodents which is alone related to their histamine-releasing effects, particularly on hypothalamic areas richly innervated by histaminergic neurons.

---

[6] Schwartz JC et al. In Psychopharmacology : the 4th Generation of progress, Raven Press Ltd, New York 1995 ; 397
[7] Lin JS. Sleep medicine Rev 2000, 4, 471
[8] Ligneau X et al. J Pharmacol Exp Ther 1998, 287, 658

The presence of H_3-receptors in vestibular nuclei or the modulation of dynamic vestibular functions in treated guinea-pigs suggest the utility of H_3-receptor antagonists as **antivertigo** or **antimotion**-sickness drugs devoid of sedating properties[9].

The anticonvulsant activity of a variety of H_3-receptor antagonists on a rodent models suggests their utility in **epilepsia**[10].

Finally, the increased level of histamine metabolites in the cerebrospinal fluid of schizophrenic patients, the dense distribution of H_3-receptors in limbic brains areas apparently involved in **schizophrenia** and the significant H_3-receptor antagonist potency of clozapine, an atypical antipsychotic compound with a poorly defined mechanism of action, all suggest that selective H_3-receptor antagonists may represent a novel class of **antipsychotic** or **antidepressive** agents.

In conclusion, it appears that the various claimed diseases involve mechanisms where H_3-receptors play a important role. Hence, ligands to this receptor such as the compounds disclosed in the present patent application are expected to exhibit a considerable potential for the treatment of these diseases.

II. Supplemental data with regard to the recited compounds

Preclinical trials which have been carried out under my supervision confirm that the compounds recited in the claims show an activity as ligands of histamine H_3 receptors, and are thus of interest in a variety of diseases involving histamine H_3 receptors.

---

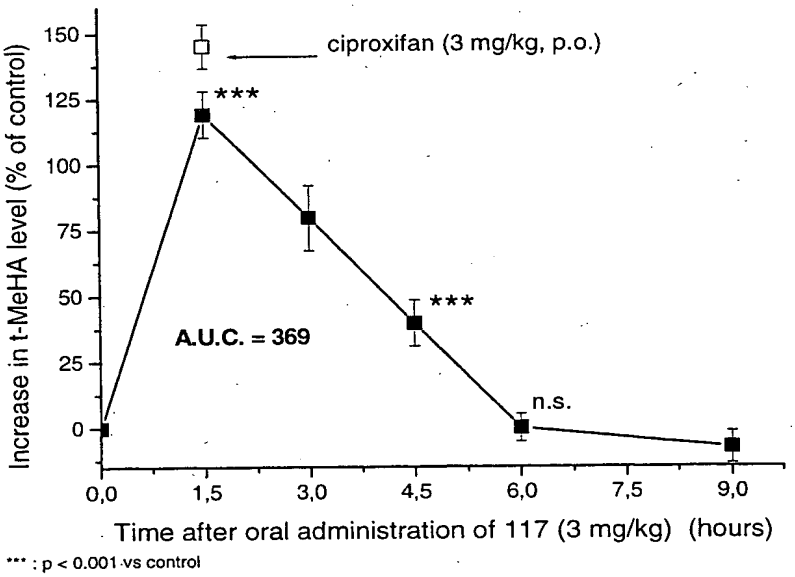
[9] Lacour M & Sterkers O. CNS Drugs 2001, 15, 853

[10] Yokoyama H. & Iinuma K. CNS Drugs 1996, 5, 321

In agreement with literature, compounds of the present invention were found to enhance histamine release from neurons in the mouse brain as evidenced by dose-dependent enhancement of the level of tele-methylhistamine, the main extracellular histamine metabolite.

Male mice received 3 mg/kg of compound 117 orally and the histamine metabolite (t-MeHA) was assayed at various times (n=24 mice per time) after gavage using an EIA derived from the method of Garbarg (Garbarg M. et al. Eur J Pharmacol 1989, 164, 1). Ciproxifan, a prototypic H_3-receptor antagonist was tested for reference.

The changes of tele-methylhistamine levels in mouse brain following oral administration of compound 117 according to the invention with time are shown in Figure 1 hereunder.



*** : $p < 0.001$ vs control

Figure 1: Changes of tele-methylhistamine levels in mouse brain following oral administration of compound 117, i.e. 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether.

In a further set of tests carried out under my supervision, various H_3-receptor antagonists were found to be active in animal models of

schizophrenia, and dementia, i.e. to block the psychomotor responses to amphetamine or dizocilpine.

Groups of 7-8 male Swiss mice received 5 mg/kg of compound 117, intraperitoneally prior to treatment with methamphetamine or dizocilpine (MK-801). Standard actimetry cages were used to measure spontaneous locomotor activity.

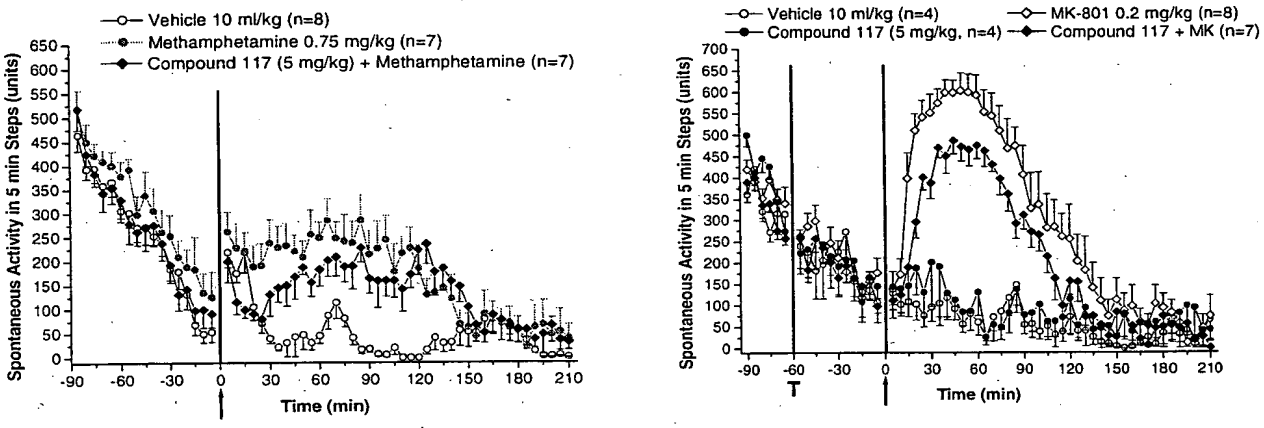


Figure 2: Effect of compound 117, i.e. 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, on methamphetamine- and dizocilpine-induced increase in spontaneous locomotor activity in mouse.

In conclusion, experimental evidence indicates that histamine H_3-receptor ligands appear as a novel class of drugs acting on a large variety of systems and thereby appear potentially useful in various therapeutic areas[11].

o-o-o-o-o

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that wilful false statements and the like so made are

[11] Meier G, Eur.J.Pharm.Sci. 2001, 13, 249 Meier G, Bioorg.Med.Chem.2002, 10, 2535

punishable by fine or imprisonment, or both, under section 1001 of Title 18 of United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this day of January 8 2003

J.C. SCHWARTZ